Effects of fluctuating physiological rhythms during prolonged EEG-fMRI studies

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Abstract

Objective—We evaluated BOLD correlates of alertness fluctuations commonly seen during prolonged EEG-fMRI studies to better define the brain areas active at different phases of vigilance and to assess the contribution of these fluctuations to the BOLD signal.

Methods—We evaluated BOLD changes specifically related to the main physiological EEG rhythms (alpha, beta, theta, delta, spindles) in 15 epilepsy patients with rare discharges (all the regressors were included in the same general linear model to improve specificity).

Results—We found a consistent effect of spindles, alpha and theta. For alpha, BOLD was positively correlated in thalami and putamen, and negatively correlated in the occipital, parietal and frontal lobes. For theta, a negative correlation was found over the parietal, temporal and frontal lobes. Spindles were correlated with a positive BOLD in thalami and putamen. Rhythm regressors added as confounds in the fMRI analysis explained at least 5% of BOLD signal variance in $6.8 \pm 8.9\%$ of gray matter voxels, a contribution which is of the order of typical changes in fMRI studies.

Conclusion—First, we found specific cerebral structures involved in each main EEG rhythm generation. Second, fluctuations of these rhythms following vigilance changes are responsible for noteworthy BOLD changes. Significance: Physiological EEG rhythms may be integrated to the analysis of EEG-fMRI in studies with fluctuation of alertness, to eliminate possible confounding factors.

Keywords

Functional MRI; Electroencephalography; Rhythm and vigilance

1. Introduction

Physiological mechanisms underlying the fluctuation of vigilance are still poorly understood. Several studies tried with different approaches to analyze them and to define different brain states (positron emission tomography (PET), single-photon emission-computed tomography, EEG, fMRI). The brain state can be defined by the characteristics of electrical brain oscillations. EEG oscillations reflect the activity of different neuronal

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networks defined by different oscillation frequencies (Lopes da Silva and Pfurtscheller, 1999) ranging between slow and fast activity (delta: 0.5–4 Hz; theta: 4–8 Hz; alpha: 8–12 Hz; beta: 12–30 Hz; gamma: >30 Hz; spindles: 11–15 Hz). The features of each oscillatory mode (extent of rhythm and location) and the transition between these oscillatory modes (Lopes da Silva and Pfurtscheller, 1999) could help to define the brain state. The analysis of rhythms (alpha, theta, delta and spindles) is used as one of the factors defining sleep stages (Rechtschaffen and Kales, 1968). At rest, fluctuations of these EEG rhythms reflect variations in alertness.

Functional magnetic resonance imaging (fMRI) measures the metabolic and hemodynamic changes (blood oxygen level-dependent, BOLD) related to neuronal activity induced by motor, sensory or cognitive tasks. With simultaneous EEG recording, BOLD correlates of EEG events can also be studied, such as epileptiform events (Gotman et al., 2006) or evoked potential (Horovitz et al., 2002; Bénar et al., 2007). In the same way, EEG-fMRI can be used to analyze the BOLD effect of each type of EEG oscillation.

This has been studied in healthy subjects with emphasis on the alpha rhythm (Goldman et al., 2002; Moosmann et al., 2003; Laufs et al., 2003a, 2006, de Munck et al., 2007; Gonçalves et al., 2006; Feige et al., 2005; Kotajima et al., 2005). With respect to the other rhythms related to sleep, such as theta (Laufs et al., 2003b; Scheeringa et al., 2007), beta (Moosmann et al., 2003; Laufs et al., 2006), delta rhythms and sleep spindles (Schabus et al., 2007), the literature is not as rich and the impact of their modulation on the BOLD signal is not as clear. However, methods used in all these studies did not distinguish the BOLD effect of each specific rhythm. Their results could mix BOLD effects of two or more rhythms if these rhythms have a correlated time course. Moreover, most studies analysed the rhythm during a short recording inside the scanner. This reduces the probability of recording fluctuations related to the state of vigilance.

Analysis in the same general linear model of all main rhythms recorded during an EEG-fMRI session could bring specific information about the structures involved in the generation of each rhythm. This method is also a way to model the brain state fluctuations in the fMRI analysis. Indeed, a current limitation of fMRI relates to the method employed to generate functional maps. The model assumes that the baseline (used as control for the functional period) is stable during the entire recording. But the vigilance state and mental processing is likely to fluctuate during the typical 20-min to 2-h recording. Even in the absence of environmental or body stimulus, endogenous functions like sleep or mental processing can modify brain activity. Variation of alertness and brain processes between events could interfere with the BOLD analysis of events.

In this work, we studied the relationships between all main EEG rhythms and BOLD in subjects with a fluctuating state of alertness to understand which brain regions are involved in their generation. We analyzed in the same general linear model the BOLD effect of each rhythm during a prolonged recording in a group of epileptic patients with rare spikes and discuss how these results compare to those obtained by others with each rhythm studied separately. We suggest that the variations of EEG rhythms modify the resting state BOLD

signal and may thus interfere with the BOLD analysis of epileptic events and of any event for which the brain state is not controlled.

2. Methods

2.1. Subjects

This study was not designed for the analysis of the BOLD effect of epileptiform spiking activity but we took the opportunity of the availability of a group of subjects who had been scanned at rest for nearly 2 h with EEG recording. Some patients have no or very rare epileptic discharges (spikes, events lasting less than 200 ms). In this class of non-severe epileptic patients, normal features of physiological brain rhythms are usually preserved. We selected 15 patients with focal epilepsy (10 males; mean age, 32.2 ± 12 years,) from our database of EEG-fMRI studies (November 2003–February 2007). The first eleven patients showing fewer than six spikes were selected (less than one spike per run) (Table 1). Only two patients (6 and 9) reached sleep stage 2 and one (patient 6) stage 3. To obtain more spindle data, we added from our database four other consecutive patients (even with more than six spikes), who presented stage 2 during the recording. In total, six recordings of patients were thus used to analyze spindles (Table 1).

All patients participated in the research study after giving written informed consent, as approved by the Research Ethics Board. All recordings followed the same protocol. No sleep deprivation was performed and no drug was administered specifically for the test.

2.2. EEG acquisition

The EEG acquisition was performed with 25 MR compatible electrodes (Ag/AgCl) placed on the scalp using the 10–10 system with a reference electrode at FCz. Two electrodes on the back recorded the electrocardiogram (EKG). The patient's head was immobilized with a pillow filled with foam microspheres (Siemens, Germany). Data were transmitted from a BrainAmp amplifier (Brain Products, Munich, Germany, 5k Hz sampling rate) via an optic fiber to the EEG monitor outside the scanner room.

2.3. fMRI acquisition

Functional images were acquired using a 1.5-T MR scanner (Siemens, Sonata, Germany). For the four patients selected for spindle analysis, we used a 3-T MR scanner (Siemens, Trio). A $T1$ -weighted anatomical acquisition was first done (1 mm slice thickness, 256 ± 256 matrix; for the 1.5-T: TE = 9.2 ms and TR = 22 ms, and for the 3-T: TE = 7.4 ms and TR = 23 ms; flip angle 30°) and used for superimposition with the functional images. The functional data were acquired in series of 6–14 runs of 6 min each using a $T2^*$ -weighted EPI sequence (voxel dimensions $5 \times 5 \times 5$, 25 slices, 64×64 matrix; for the 1.5-T: TE = 50 ms and TR = 3 s; and for the 3-T: TE = 30 ms and TR = 1750 ms; flip angle 90°). Patients received the instruction not to move, to keep the eyes closed and to be relaxed during the fMRI session. They were allowed to fall asleep.

2.4. EEG processing

Brain Vision Analyser software (Brain Products) was used for removal of the gradient artifact and EEG filtering. This software uses the method of Allen et al. (2000), based on the subtraction of the average signal obtained during the scanner artifact. A 50-Hz low-pass filter was also applied to remove the remaining artifact. The ballistocardiogram (BCG) artifact was removed by independent component analysis (ICA) and the components were examined by an experienced electroencephalographer (Béнар et al., 2003). ICA components were ordered according to their level of correlation with the BCG. Only the components clearly related to the BCG artifact but not including physiological signal were removed. Other methods of BCG artifact correction (the Optimal Basis Set by Debener et al. (2007) and the pulse artifact correction by R-peak detection by Allen et al. (2000)) were also evaluated on our data. They both left residual artifacts that could interfere in our study of EEG rhythms, which is based on the EEG power in each frequency band.

For each patient, we analyzed the entire EEG in one block (runs were concatenated). We analyzed simultaneously the power variations of the alpha, beta, theta and delta bands during the entire recording. The following bipolar montage was used: P3–O1, T5–O1, P4–O2 and T6–O2 for the alpha band and T3–T5, T4–T6, F3–P3, F4–P4 for the other bands. The power corresponding to each EPI image was computed by averaging the spectra from three 4-s windows of EEG (2048 points at 500 Hz) with 50% overlap, making an 8-s section. This section was centered at the middle of each frame. These spectra were averaged over the channels enumerated above. For alpha, we took into account inter-individual variability by selecting the frequency band for each subject. For every patient, we examined the spectrum in the alpha range at different times of the recording. We defined the individual alpha band as the band which contained all the alpha peaks in the recording. With this method (instead of a predetermined frequency band) we avoided contamination from frequencies not related with the alpha of the subject and did not miss part of that activity. Rather than the usual 13–30 Hz beta band, we defined the beta band as more than the double (22–30 Hz) of the alpha peak, to avoid the frequent second harmonic of alpha activity in the beta band (Niedermeyer and Lopes da Silva, 2005). The other frequency bands were fixed: theta (3.5–7.5 Hz) and delta (0.5–3.5 Hz). A neurologist reviewed the EEG to mark all epileptic events and to mark spindles (in the 11-to 15-Hz band). To avoid interaction of interictal events or remaining small motion artifacts with the power variation analysis, we replaced the EEG during these events with a signal obtained by interpolating between the EEG before and after the event. The mean and standard deviation of the power in each band were expressed in $\mu\text{V}^2/\text{Hz}$.

2.5. fMRI processing

EPI images were motion corrected and smoothed (6 mm full-width at half-maximum) using the software from the Brain Imaging Center of the Montreal Neurological Institute (<http://www.bic.mni.mcgill.ca/software/>). Temporal autocorrelations were accounted for by fitting an AR model of order 1 according to the methods of Worsley et al. (2002), and low frequency drifts were modeled with a third-order polynomial fitted to each run.

The t -maps (maps of the t statistic) were obtained using the power fluctuations in each band and the timings of the spindles as events in the fMRI analysis (fMRIstat, Worsley et al.,

2002). The power variations of each rhythm and the spindle events were convolved with the standard hemodynamic response function (HRF) (Glover, 1999) and used as a regressor in a single general linear model. A statistical t -map was obtained for each rhythm. Strength of the correlation was defined by the t -value (effect of each regressor in the general linear model). For $p = 0.001$ (uncorrected), the corresponding t is $+3.1$. An extent threshold of five contiguous voxels is then applied in order to obtain an overall threshold of $p < 0.01$ corrected for multiple comparisons using the minimum given by a Bonferroni correction and random field theory (Worsley et al., 2002). For t -map figures, we used a yellow–red scale (t -value: $+3.1$ to $+t_{\max}$) for positive correlation and a white–blue scale (t -value: $-t_{\max}$ to -3.1) for negative correlation. Only the correlations obtained in the brain were considered. BOLD correlations found in vessels or ventricular areas were not reported, since they are not helpful in understanding the location of rhythm generators.

A group analysis was performed across subjects for each rhythm. The anatomical MRIs of each patient were co-registered to the ICBM152 averaged brain template with a rigid-body transformation using local software. The transformation parameters were then used to resample the fMRI results from each subject onto the common template. These individual results were then combined in a random-effects linear model according to the methods of Worsley et al. (2002). Specifically, the model is fitted by restricted maximum likelihood, with spatial smoothing of the ratio of random-effect to fixed-effect variance estimates to compensate for the low degrees of freedom of the model due to the relatively low number of patients in the study. The resulting t -maps were thresholded at $|t| > 3.1$ ($p < 0.001$ uncorrected), with a spatial extent threshold applied on the resulting clusters to obtain a p -value less than 0.05, corrected by random field theory. Moreover, the analysis of spindles was restricted over a region-of-interest (ROI) encompassing the thalami and putamen because, in group analyses over the whole brain, BOLD responses in small structures even consistently observed in every individual can be non significant due to smoothing (Worsley et al., 2002). According to studies demonstrating the role of putamen and thalami in spindle generation (Steriade and Llinás, 1988; Steriade and Amzica, 1998; Schabus et al., 2007), we restricted the group analysis to this ROI.

To estimate the potential improvement of results obtained in prolonged fMRI studies using this new method (all rhythms regressors merged in the same general linear model), we calculated changes of the signal to noise ratio (SNR). We measured the variance of the BOLD explained by our regressors all together in gray matter. We used the standard ICBM gray matter template (Mazziotta et al., 2001). We generated F tests for each subject to compute the significance of the reduction of the error variance provided by modeling the EEG rhythms.

3. Results

In Fig. 1, results of the gradient artifact correction and BCG removal by ICA are shown. While the low-pass filter (cut-off 50 Hz) and the BCG correction by ICA could theoretically reduce the power of the frequency bands under study, the physiological rhythms were largely preserved after the entire preprocessing (Fig. 2). Only ICA components with BCG artifact were removed and components with physiological rhythms were preserved. Even if some

EEG power was removed, the time fluctuations of the rhythms were not altered (Fig. 3) and only these fluctuations are critical in the analysis.

3.1. Correlation between BOLD and the spontaneous variations in alpha

A specific alpha band could be determined for every patient fluctuating between 8.8 and 12 Hz (Table 1). A clear inter-subject and intra-subject variability of the alpha power was observed (Table 2, mean $4.09 \pm 3.6 \mu\text{V}^2/\text{Hz}$).

Analysis of correlation between BOLD and alpha time course gave consistent results across subjects (Table 2, Fig. 4). In the majority (7/11), the positive correlation involved the thalami with a large maximum *t*-value (mean: 7.6, range: 3.3–15.1). The anterior and posterior cingulate areas, left and right inferior frontal areas, left parietal and bitemporal areas were in small number of cases activated with the increase of alpha power. The negative correlation was more extensive than the positive correlation, involving the occipital lobe in 8/11 cases (mean max. *t*-value: -9.96, range: -5.2 to -16.8). The parietal, frontal and temporal areas were also often involved. In 6/11 patients, parietal and frontal regions were involved in a negative correlation at the same time as the occipital lobe. In a few cases a negative correlation over the anterior and the posterior cingulate areas was noticed.

A group analysis was performed with all patients (Table 3). One large cluster was positively correlated with alpha power. It was located bilaterally over the thalami and putamen (Fig. 4). A negative correlation was observed over two clusters. The largest was located bilaterally over the cuneus, precuneus, middle occipital gyrus, inferior temporal gyrus and in the left side over the inferior parietal lobule, the precentral gyrus, the inferior frontal gyrus and the middle frontal gyrus. The second cluster showed a significant negative correlation over the right hemisphere on the inferior parietal lobule, paracentral parietal lobule, precentral gyrus, inferior frontal gyrus and middle frontal gyrus. Taken together, these two clusters of negative correlation corresponded to largely symmetrical regions.

3.2. Correlation between BOLD and the spontaneous variations in beta

The mean beta power was low for every patient ($0.25 \pm 0.19 \mu\text{V}^2/\text{Hz}$) (Table 2). There was no difference of power value between each subject, and this power fluctuated in some recordings only (average of the SD: $0.15 \pm 0.15 \mu\text{V}^2/\text{Hz}$). Even if the high range of frequency studied could explain the low power value compared to the other bands, the absence of power modulation suggests that the EEG of our patients was not affected by the beta rhythm.

Correlation between BOLD and modulation of the beta power was found only in patient 6. A positive correlation was observed in the left parietal, frontal and temporal areas, and a negative correlation in the occipital lobe.

The group analysis did not result in any significant cluster.

3.3. Correlation between BOLD and the spontaneous variations in theta

The mean theta power was variable between patients ($5.4 \pm 7 \mu\text{V}^2/\text{Hz}$) (Table 2). The positive correlation between the BOLD signal and the theta power time course involved

irregularly different brain regions in small clusters: thalami and putamen, right inferior frontal area, occipital lobe, left and right inferior parietal lobules and anterior cingulate area, and posterior cingulate area, left inferior frontal lobule and left temporal area. Regarding the negative correlation, involved regions were more extensive and constant than for positive correlation (Fig. 5 and Table 2): bilateral inferior parietal lobule and left inferior frontal gyrus, right inferior frontal gyrus, occipital lobe and bilateral superior temporal gyri, anterior cingulate area and posterior cingulate area. In 4/11 patients, a negative correlation was observed over the occipital, parietal, frontal and temporal areas together.

The group analysis failed to find a significant cluster.

3.4. Correlation between BOLD and the spontaneous variations in delta

The mean delta power was highly variable between patients ($24.6 \pm 55.6 \mu\text{V}^2/\text{Hz}$) (Table 2) and depended on the stage of sleep reached (patient 6 with sleep stage 3, presented larger mean delta power ($191.26 \mu\text{V}^2/\text{Hz}$)). As delta waves have larger amplitude than the other bands, patients with low power value and with few variations could be considered as showing no delta rhythm.

No correlation between BOLD signal and delta power time course was obtained for 3/11 subjects (Table 2). Areas concerned by the positive correlation were the bilateral frontal, temporal and parietal lobes, the occipital lobe, the anterior cingulate area and thalami. A negative correlation was only observed for 3/11 patients. Two had a negative correlation over the occipital lobe and one over the left and right frontal lobes and the right temporal lobe.

No significant cluster was present in the group analysis.

3.5. Correlation between BOLD and sleep spindles

Each of the 6 patients presented at least 10 spindles suggesting that stage 2 of sleep was reached during a relative stable and prolonged period. BOLD analysis showed activation in 4/6 subjects and deactivation for 3/6 subjects (Table 2). Activation was observed over the thalami, the bilateral putamen, the bilateral caudate nucleus, the right and the left inferior temporal gyrus and both hippocampi (Fig. 6). Deactivation was more inconsistent than the activation and involved in two patients the left parietal area and the left frontal lobe, and in one both occipital lobes, the right frontal and left temporal lobes.

We defined two ROIs (thalami and bilateral putamen) for group analysis. There was no significant negative BOLD related to the spindles (Fig. 6), but we observed a significant activation over four different clusters: left and right lateral anterior parts of the thalamus, left and right putamen.

3.6. BOLD signal variance explained by rhythms regressors

Considering all the subjects, the average of the maxima of the BOLD signal variance explained by our regressors was $20.4 \pm 6\%$. This maximum involved mostly voxels in the occipital and parietal lobes. Application of our regressors explained at least 5% of the BOLD signal variance in $6.8 \pm 8.9\%$ of voxels located in gray matter (mean of the gray matter volume: 6689 ± 548 voxels).

4. Discussion

The impact of each physiological rhythm (alpha, beta, theta and delta) on the BOLD signal was estimated using the power time course of each frequency band and the time of spindle occurrence. Compared to previous studies, BOLD responses were more specific of each rhythm in our study, as a result of using a common GLM analysis. For alpha, theta and spindles we extracted a clear spatial pattern which can help to understand their generators. Finally, in these prolonged recordings, rhythm regressors added as confounds in the GLM can explain a part of the BOLD signal variance. This new method could improve results of cognitive, motor and epileptic fMRI studies with prolonged recording.

Prolonged recordings in fMRI are limited by physiological attention and vigilance fluctuations. However, the duration of the test is necessary to record enough events and to allow statistical analysis. Modeling of brain state fluctuations would be useful to obtain accurate results of many fMRI studies. In this study, we hypothesized that a particular rhythm is generated in the same place, independently of the state in which it occurs. In fact our point of view is that it is the combination of different physiological rhythms that define the brain state. We used the fluctuations of main physiological rhythms to model these brain state fluctuations.

Most EEG-fMRI studies done on rhythms analysed separately (in different GLM analyses) BOLD changes related to fluctuations of each frequency band. It gave useful information about neuronal networks involved in each case. However, different rhythms can coexist during the same vigilance state at different locations and different rhythms could exist at the same location during different states of vigilance (Varela et al., 2001; Steriade, 2001). Results obtained in these studies for one rhythm could be confounded by the BOLD effect of other rhythms. In particular, results could include BOLD changes common to several rhythms (if their fluctuations are correlated) and decreasing BOLD responses specific to a given rhythm (if their fluctuations are not correlated). In our work we included in the same GLM the regressors for every rhythm. Analysis of one rhythm is done using fluctuations of the other bands as confounds, thus improving, on theoretical grounds, the specificity of the negative and positive BOLD correlations for each rhythm. Differences between *t*-maps obtained with separate GLM analyses and with our single analysis reflect the variable degree of correlation between fluctuations of all these rhythms. Only the specific BOLD changes of the rhythm studied are emphasized with the single analysis (see example Fig. 7). This model including all rhythms regressors in the same analysis is also closer to the normal brain physiology compared to each separate rhythm model. Compared to previous studies, we analyzed rhythm fluctuations of in a prolonged recording, providing a better sampling of fluctuating rhythms related to different vigilance states. In a 20-min session, drowsiness or light sleep occurs less frequently and rhythms related to these particular states could be difficult to analyze.

4.1. Cerebral correlates of alpha

In our epilepsy patients, characteristics of the alpha rhythm (frequency, reactivity, and location) were within the normal range. As Laufs et al. (2003a, 2006) and Gonçalves et al. (2006), we found inter-subject variability, in accordance with variations of alpha

characteristics seen on EEG studies (Feshchenko et al., 2001). Nevertheless we found a common BOLD pattern involving the same brain areas. Most patients showed a positive correlation in the thalami extending to the putamen. These areas were strongly correlated in the group analysis. Negative correlations were seen in occipital lobes and other neocortical areas such as parietal (inferior and paracentral parietal lobules) and frontal regions (precentral, inferior frontal and middle frontal gyri).

With our method, we strengthen results reported in the literature. Most studies observed a positive correlation with alpha power in the thalami and a strong negative correlation in the occipital, parietal and frontal lobes (Goldman et al., 2002; Moosmann et al., 2003; Feige et al., 2005; Gonçalves et al., 2006; Laufs et al., 2006; de Munck et al., 2007; Kotajima et al., 2005). The other rhythms did not influence the alpha results. The specificity of BOLD changes in relation to alpha fluctuations is easy to understand when considering the high t -value of negative and positive correlation obtained in previous studies. These results confirm animal studies (Lopes da Silva and Storm van Leeuwen, 1997; Steriade et al., 1990) reporting two different components in the generation of the alpha rhythm: the rhythmic thalamic activity and a cortico-cortical component that contributes to the generation of a cortical domain of alpha and its propagation over the cortex. Positive correlation of BOLD in the thalami could be explained by the rhythmic depolarization leading to repetitive bursts of action potential. The meaning of the negative correlation in cortical areas is less clear. BOLD decrease could reflect either a decrease (Shmuel et al., 2002, 2006; Stefanovic et al., 2004) or an increase (Harel et al., 2002; Schridde et al., 2007) of neuronal activity, depending on the balance between oxygen consumption and oxygen supply. The alpha rhythm has been described as an 'idling' state, reflecting a cortical disengagement from inputs of the body and environment. BOLD decrease in occipital lobes therefore suggests a decrease of neuronal activity with low local oxygen consumption (Moosmann et al., 2003; Sotero and Trujillo-Barreto, 2008).

4.2. Cerebral correlates of theta

BOLD changes related to the theta rhythm were already reported by Gonçalves et al. (2006) and Laufs et al. (2006). They showed an influence of this rhythm on alpha related BOLD effect. Our results regarding the effect of theta on the BOLD signal could at first be puzzling. The positive correlation was heterogeneous and inconsistent, but most patients showed a similar pattern of negative correlation, involving associative areas (inferior parietal lobule, inferior frontal gyrus, superior temporal gyrus), the occipital lobe and sometimes the limbic system including the anterior cingulate area. Group analysis failed to demonstrate a significant cluster. However, the volume of cortical structures involved especially by the negative correlation and the t -values were small and the group analysis method may not reveal such regions as significant due to smoothing (Worsley et al., 2002). Individual results were coherent with the general finding of a decrease of brain activity during sleep stages compared to wakefulness or REM sleep (Kaufmann et al., 2006; Fukunaga et al., 2006).

BOLD changes related to theta have only been evaluated in two studies. Laufs et al. (2003b) did not find a correlation between theta and BOLD in 20-min recordings. During a 10-min session of resting state (without sleep), Scheeringa et al. (2007) analyzed the spontaneous

middle frontal theta rhythm, which is related to cognitive and attention processes during wakefulness (Sammer et al., 2007; Onton et al., 2005). As in several of our subjects, a negative correlation was found over the inferior frontal cortex, middle temporal gyrus, inferior parietal lobule, precuneus and posterior cingulate cortex. In our study, we potentially recorded and analyzed different types of theta rhythms (during wakefulness and during light sleep) characterized by different generators (Cantero et al., 2003; Nishida et al., 2004). However, in our condition of recording, without specific cognitive task, the theta rhythm specifically related to light sleep was more likely to be predominant. Whatever the type of theta rhythm analyzed (our study, Scheeringa et al., 2007; Kaufmann et al., 2006; Fukunaga et al., 2006), structures negatively correlated with BOLD were similar. Theta seems related to the default mode network (Raichle et al., 2001). Compared to the other studies (Laufs et al., 2003b; Scheeringa et al., 2007), because we integrated in the same GLM each rhythm regressor, we can ensure that this pattern is more specific of theta and less correlated with other rhythms. Metabolism of the default-mode areas decreases with loss of consciousness as showed by studies on sedation (Kiviniemi et al., 2005) and during vegetative state (Laureys, 2004). It confirms that the theta rhythm reflects a rest state of the brain with a reduced activity of all limbic and associative areas. A reduction of alertness and of activity of the areas responsible for environmental stimuli reaction allows a deepening of sleep until the stage SWS.

4.3. Cerebral correlates of spindles

In our six patients, we found a positive correlation between BOLD and spindles in the thalami and putamen. Group and individual analysis failed to show a consistent negative correlation. These results are difficult to compare to those of the literature because cerebral correlates of spindles were mostly indirectly studied by sleep studies that encompassed all NREM or stage 2. Only one recent paper by Schabus et al. (2007) reported hemodynamic modifications related specifically to spindles. They also showed a common positive correlation with BOLD in the lateral part of the thalami. These results and ours corroborate studies done with intracerebral animal recordings that describe the role of the thalami and especially the reticular nucleus in spindle generation (Steriade and Llinás, 1988; Steriade and Amzica, 1998).

In addition, we showed an involvement of the putamen (mostly posterior). In two cases the caudate nucleus was also involved. BOLD activation of the striatum during spindles could be the reflection of its strong interconnectivity with the thalamus and the thalamocortical pathway (Braun et al., 1997; Maquet, 2000; Dang-Vu et al., 2005). Specific studies should be conducted to better understand the role of this structure in different sleep processes.

4.4. Cerebral correlates of delta

Most patients did not sleep deeply. Only one reached stage 3 characterized by delta waves. Fluctuation of delta power in the other cases was very small and was not related to the delta waves observed during sleep. Looking at individual results, delta power was more positively correlated with BOLD than negatively. But this pattern was different for each patient. Heterogeneous cortical areas (frontal, parietal and temporal) were involved. Even the large fluctuations of delta power observed in patient 6 were not correlated with BOLD

modulation. The difficulty to obtain a clear pattern of negative and positive correlation could be explained by the heterogeneity of different delta rhythms present during a prolonged recording. Additional features (as duration of the bursts) should be included to specifically study the delta rhythm related to deep sleep stage. We could not corroborate previous studies using PET (Hofle et al., 1997; Dang-Vu et al., 2005) or EEG-fMRI (Kaufmann et al., 2006) during SWS showing a global BOLD decrease in bilateral frontal and associative areas, cingulate cortex and sometimes in the thalami.

4.5. Cerebral correlates of beta

In most patients, no specific area was involved by BOLD changes. This differs from the results presented in the literature (Moosmann et al., 2003; Laufs et al., 2003b). During wakefulness in short recordings, they showed an involvement of cortical areas concordant with cognitive and multisensory functions of the usual beta rhythm. This difference with our results could be explained by several factors. We excluded the low beta band from our analysis to avoid contamination by alpha harmonics, which can represent a large amount of energy. Using a single GLM study, we analyzed specifically BOLD effect of beta rhythm fluctuations; the other studies cannot distinguish in their results the possible interference from other rhythms. Our recording was longer (2h) and we explored beta rhythm during wakefulness and sleep onset. The beta rhythm associated with sensorimotor and cognitive processing was then logically poorly represented as reflected by low EEG power and small fluctuations of beta in our subjects.

Contrary to the literature, our study was performed on epileptic subjects, who of course were taking antiepileptic drugs. We tried to reduce the disease effect on our results in selecting patients with very small number of epileptiform events and with a normal background EEG. We also analyzed the EEG time course of each rhythm on the 'normal' side (contralateral to the epileptiform activity). However these patients were taking antiepileptic drugs. The effect of the drugs on EEG signal is variable depending on the type and on the dose. Some of these drugs are known to increase high-frequency band activity (Huang and Shen, 1997; Salinsky et al., 1994). It is unclear how they can affect the other bands. However, the goal of this work was to define the specific brain structures involved during each main brain rhythm generation. Antiepileptic drugs could modify the relative proportion of one rhythm to another, but rhythms should keep their normal features. We verified for each patient that each rhythm in its typical location fluctuated normally (for example, alpha power decreased when the theta was appearing during light sleep). BOLD correlates obtained for each rhythm should be similar in a healthy population. In fact our results were in agreement with those observed in the normal population in previous studies; this confirms the validity of our population.

Specific BOLD correlation related to each physiological rhythm was obtained using regressors from all rhythms in the same GLM. This is also a way to model fluctuations of the vigilance state during prolonged recordings. In our subjects, application of these regressors help to reduce 5% of the BOLD signal variance in $6.8 \pm 8.9\%$ of voxels located in gray matter. BOLD baseline is probably associated with other variations such as respiratory or cardiac changes. Adding 21 regressors modeling the cardiac signal, Liston et al. (2006)

observe a variance reduction of $4.36 \pm 2.79\%$ in gray matter. Similarly, BOLD fluctuations correlated with physiological rhythms represent a non-negligible fraction of baseline fluctuation especially in posterior areas which could be involved in spike generation. Further studies should be conducted to explore the effect of this method on BOLD responses related to tasks or epileptic events during prolonged recording.

This is the first study analyzing the specific BOLD effect of each main physiological rhythm using a common GLM analysis. We first strengthen published results on alpha rhythm. We found a specific correlation between the ‘default mode’ pattern and theta rhythm fluctuations. For spindles, we corroborated the thalamic activation (Schabus et al., 2007) and observed additionally an implication of the putamen. These findings help to assess the role of brain structures in each different physiological rhythm. We showed that during a prolonged recording, variations of the alpha, theta and spindle rhythms were related to significant BOLD fluctuations. These fluctuations were dissociated from tasks or epileptic events; they were part of the BOLD “baseline”. A part of the BOLD signal variance was explained by these fluctuations especially in the posterior brain area. Current fMRI studies with prolonged recordings for specific tasks or epileptic events are limited by the definition of the BOLD baseline. The impact of physiological rhythm modulation on the analysis of BOLD responses related to tasks or epileptic events should be analyzed in the future. The accuracy of fMRI studies may be improved.

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References

- Allen PJ, Josephs O, Turner R. A method for removing imaging artifact from continuous EEG recorded during functional MRI. *Neuroimage*. 2000; 12:230–9. [PubMed: 10913328]
- Bénar C, Aghakhani Y, Wang Y, Izenberg A, Al-Asmi A, Dubeau F, et al. Quality of EEG in simultaneous EEG-fMRI for epilepsy. *Clin Neurophysiol*. 2003; 114:569–80. [PubMed: 12705438]
- Bénar CG, Schön D, Grimault S, Nazarian B, Burle B, Roth M, et al. Single-trial analysis of oddball event-related potentials in simultaneous EEG-fMRI. *Hum Brain Mapp*. 2007; 28:602–13. [PubMed: 17295312]
- Braun AR, Balkin TJ, Wesenten NJ, Carson RE, Varga M, Baldwin P, et al. Regional cerebral blood flow throughout the sleep-wake cycle. An $H_2(15)O$ PET study. *Brain*. 1997; 120:1173–97. [PubMed: 9236630]
- Cantero JL, Atienza M, Stickgold R, Kahana MJ, Madsen JR, Kocsis B. Sleep-dependent theta oscillations in the human hippocampus and neocortex. *J Neurosci*. 2003; 23:10897–903. [PubMed: 14645485]
- Dang-Vu TT, Desseilles M, Laureys S, Degueldre C, Perrin F, Phillips C, et al. Cerebral correlates of delta waves during non-REM sleep revisited. *Neuroimage*. 2005; 28:14–21. [PubMed: 15979343]
- de Munck JC, Gonçalves SI, Huijboom L, Kuijter JP, Pouwels PJ, Heethaar RM, et al. The hemodynamic response of the alpha rhythm: an EEG/fMRI study. *Neuroimage*. 2007; 35:1142–51. [PubMed: 17336548]
- Debener S, Strobel A, Sorger B, Peters J, Kranczioch C, Engel AK, et al. Improved quality of auditory event-related potentials recorded simultaneously with 3-T fMRI: removal of the ballistocardiogram artefact. *Neuroimage*. 2007; 34:587–97. [PubMed: 17112746]

- Feige B, Scheffler K, Esposito F, Di Salle F, Hennig J, Seifritz E. Cortical and subcortical correlates of electroencephalographic alpha rhythm modulation. *J Neurophysiol.* 2005; 93:2864–72. [PubMed: 15601739]
- Feshchenko VA, Reinsel RA, Veselis RA. Multiplicity of the alpha rhythm in normal humans. *J Clin Neurophysiol.* 2001; 18:331–44. [PubMed: 11673699]
- Fukunaga M, Horovitz SG, van Gelderen P, de Zwart JA, Jansma JM, Ikonomidou VN, et al. Large-amplitude, spatially correlated fluctuations in BOLD fMRI signals during extended rest and early sleep stages. *Magn Reson Imaging.* 2006; 24:979–92. [PubMed: 16997067]
- Glover GH. Deconvolution of impulse response in event related BOLD fMRI. *Neuroimage.* 1999; 9:416–29. [PubMed: 10191170]
- Goldman RI, Stern JM, Engel J Jr, Cohen MS. Simultaneous EEG and fMRI of the alpha rhythm. *Neuroreport.* 2002; 13:2487–92. [PubMed: 12499854]
- Gonçalves SI, de Munck JC, Pouwels PJ, Schoonhoven R, Kuijter JP, Maurits NM, et al. Correlating the alpha rhythm to BOLD using simultaneous EEG/fMRI: inter-subject variability. *Neuroimage.* 2006; 30:203–13. [PubMed: 16290018]
- Gotman J, Kobayashi E, Bagshaw AP, Benar CG, Dubeau F. Combining EEG and fMRI: a multimodal tool for epilepsy research. *J Magn Reson Imaging.* 2006; 23:906–20. [PubMed: 16649203]
- Harel N, Lee SP, Nagaoka T, Kim DS, Kim SG. Origin of negative blood oxygenation level-dependent fMRI signals. *J Cereb Blood Flow Metab.* 2002; 22:908–17. [PubMed: 12172376]
- Hofle N, Paus T, Reutens D, Fiset P, Gotman J, Evans AC, et al. Regional cerebral blood flow changes as a function of delta and spindle activity during slow wave sleep in humans. *J Neurosci.* 1997; 17:4800–8. [PubMed: 9169538]
- Horovitz SG, Skudlarski P, Gore JC. Correlations and dissociations between BOLD signal and P300 amplitude in an auditory oddball task: a parametric approach to combining fMRI and ERP. *Magn Reson Imaging.* 2002; 20:319–25. [PubMed: 12165350]
- Huang ZC, Shen DL. Studies on quantitative beta activity in EEG background changes produced by intravenous diazepam in epilepsy. *Clin Electroencephalogr.* 1997; 28:172–8. [PubMed: 9241472]
- Kaufmann C, Wehrle R, Wetter TC, Holsboer F, Auer DP, Pollmächer T, et al. Brain activation and hypothalamic functional connectivity during human non-rapid eye movement sleep: an EEG/fMRI study. *Brain.* 2006; 129:655–67. [PubMed: 16339798]
- Kiviniemi VJ, Haanpää H, Kantola JH, Jauhainen J, Vainionpää V, Alahuhta S, et al. Midazolam sedation increases fluctuation and synchrony of the resting brain BOLD signal. *Magn Reson Imaging.* 2005; 23:531–7. [PubMed: 15919598]
- Kotajima F, Meadows GE, Morrell MJ, Corfield DR. Cerebral blood flow changes associated with fluctuations in alpha and theta rhythm during sleep onset in humans. *J Physiol.* 2005; 568:305–13. [PubMed: 16002438]
- Laufs H, Kleinschmidt A, Beyerle A, Eger E, Salek-Haddadi A, Preibisch C, et al. EEG-correlated fMRI of human alpha activity. *Neuroimage.* 2003a; 19:1463–76. [PubMed: 12948703]
- Laufs H, Krakow K, Sterzer P, Eger E, Beyerle A, Salek-Haddadi A, et al. Electroencephalographic signatures of attentional and cognitive default modes in spontaneous brain activity fluctuations at rest. *Proc Natl Acad Sci USA.* 2003b; 100:11053–8. [PubMed: 12958209]
- Laufs H, Holt JL, Elfont R, Krams M, Paul JS, Krakow K, et al. Where the BOLD signal goes when alpha EEG leaves. *Neuroimage.* 2006; 31:1408–18. [PubMed: 16537111]
- Laureys S. Functional neuroimaging in the vegetative state. *NeuroRehabilitation.* 2004; 19:335–41. [PubMed: 15671588]
- Liston AD, Lund TE, Salek-Haddadi A, Hamandi K, Friston KJ, Lemieux L. Modelling cardiac signal as a confound in EEG-fMRI and its application in focal epilepsy studies. *Neuroimage.* 2006; 30:827–34. [PubMed: 16343949]
- Lopes da Silva FH, Storm van Leeuwen W. The cortical source of the alpha rhythm. *Neurosci Lett.* 1997; 6:237–41.
- Lopes da Silva, FH., Pfurtscheller, G. Basic concepts on EEG synchronization and desynchronization. In: Pfurtscheller, G., Lopes da Silva, FH., editors. *Event-related desynchronization. Handbook of electroencephalography and clinical neurophysiology.* Vol. 6. Amsterdam: Elsevier; 1999. p. 3-11.

- Maquet P. Functional neuroimaging of normal human sleep by positron emission tomography. *J Sleep Res.* 2000; 9:207–31. [PubMed: 11012860]
- Mazziotta J, Toga A, Evans A, Fox P, Lancaster J, Zilles K, et al. A probabilistic atlas and reference system for the human brain: international consortium for brain mapping (ICBM). *Philos Trans Roy Soc Lond B Biol Sci.* 2001; 356:1293–322. [PubMed: 11545704]
- Moosmann M, Ritter P, Krastel I, Brink A, Thees S, Blankenburg F, et al. Correlates of alpha rhythm in functional magnetic resonance imaging and near infrared spectroscopy. *Neuroimage.* 2003; 20:145–58. [PubMed: 14527577]
- Niedermeyer, E., Lopes da Silva, F. *Electroencephalography: basic principles, clinical applications and related fields.* 5. Baltimore, MD: Williams and Wilkins; 2005. p. 85-107.
- Nishida M, Hirai N, Miwakeichi F, Maehara T, Kawai K, Shimizu H, et al. Theta oscillation in the human anterior cingulate cortex during all-night sleep: an electrocorticographic study. *Neurosci Res.* 2004; 50:331–41. [PubMed: 15488296]
- Onton J, Delorme A, Makeig S. Frontal midline EEG dynamics during working memory. *Neuroimage.* 2005; 27:341–56. [PubMed: 15927487]
- Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proc Natl Acad Sci USA.* 2001; 98:676–82. [PubMed: 11209064]
- Rechtschaffen, A., Kales, A. *A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects.* Washington, DC: US Public Health Service, US Government Printing Office; 1968.
- Salinsky MC, Oken BS, Morehead L. Intraindividual analysis of antiepileptic drug effects on EEG background rhythms. *Electroencephalogr Clin Neurophysiol.* 1994; 90:186–93. [PubMed: 7511500]
- Sammer G, Blecker C, Gebhardt H, Bischoff M, Stark R, Morgen K, et al. Relationship between regional hemodynamic activity and simultaneously recorded EEG-theta associated with mental arithmetic-induced workload. *Hum Brain Mapp.* 2007; 28:793–803. [PubMed: 17080437]
- Schabus M, Dang-Vu TT, Albouy G, Balet E, Boly M, Carrier J, et al. Hemodynamic cerebral correlates of sleep spindles during human non-rapid eye movement sleep. *Proc Natl Acad Sci USA.* 2007; 104:13164–9. [PubMed: 17670944]
- Scheeringa R, Bastiaansen MC, Petersson KM, Oostenveld R, Norris DG, Hagoort P. Frontal theta EEG activity correlates negatively with the default mode network in resting state. *Int J Psychophysiol.* 2007;12.
- Schridde U, Khubchandani M, Motelow JE, Sanganahalli BG, Hyder F, Blumenfeld H. Negative BOLD with Large Increases in Neuronal Activity. *Cereb Cortex.* 2007;5.
- Shmuel A, Yacoub E, Pfeuffer J, Van de Moortele PF, Adriany G, Hu X, et al. Sustained negative BOLD, blood flow and oxygen consumption response and its coupling to the positive response in the human brain. *Neuron.* 2002; 36:1195–210. [PubMed: 12495632]
- Shmuel A, Augath M, Oeltermann A, Logothetis NK. Negative functional MRI response correlates with decreases in neuronal activity in monkey visual area V1. *Nat Neurosci.* 2006; 9:569–77. [PubMed: 16547508]
- Sotero RC, Trujillo-Barreto NJ. Biophysical model for integrating neuronal activity, EEG, fMRI and metabolism. *Neuroimage.* 2008; 39:290–309. [PubMed: 17919931]
- Stefanovic B, Wernking JM, Pike GB. Hemodynamic and metabolic responses to neuronal inhibition. *Neuroimage.* 2004; 22:771–8. [PubMed: 15193606]
- Steriade M, Llinás RR. The functional states of the thalamus and the associated neuronal interplay. *Physiol Rev.* 1988; 68:649–742. [PubMed: 2839857]
- Steriade M, Gloor P, Llinás RR, Lopes de Silva FH, Mesulam MM. Report of IFCN committee on basic mechanisms. Basic mechanisms of cerebral rhythmic activities. *Electroencephalogr Clin Neurophysiol.* 1990; 76:481–508. [PubMed: 1701118]
- Steriade M, Amzica F. Coalescence of sleep rhythms and their chronology in corticothalamic networks. *Sleep Res Online.* 1998; 1:1–10. [PubMed: 11382851]
- Steriade M. Impact of network activities on neuronal properties in corticothalamic systems. *J Neurophysiol.* 2001; 86:1–39. [PubMed: 11431485]

- Varela F, Lachaux JP, Rodriguez E, Martinerie J. The brainweb: phase synchronization and large-scale integration. *Nat Rev Neurosci.* 2001; 2:229–39. [PubMed: 11283746]
- Worsley KJ, Liao CH, Aston J, Petre V, Duncan GH, Morales F, et al. A general statistical analysis for fMRI data. *Neuroimage.* 2002; 15:1–15. [PubMed: 11771969]

Fig. 1. EEG signal processing. (a) EEG recorded during EPI session with the gradient artifact. (b) EEG signal (subset of channels) obtained after offline correction of the gradient artifact with a subtraction method and low pass filtering (<50 Hz). The BKG artifact alters the EEG. (c) Final EEG signal obtained after BKG removal by ICA. The alpha rhythm is clearly visible in this example. (d) ICA decomposition of the EEG signal from (b); we removed the components containing the BKG artifact (F12, F13, F18, F09, and F14) and sometimes those still dominated by residual gradient artifact (F24) in order to obtain the EEG shown in (c). The physiological rhythms were largely preserved after the entire preprocessing.

Fig. 2.

Final EEG obtained after gradient artifact and BKG artifact removal. EEGs at times when the different physiological rhythms analyzed in this study dominate.

Fig. 3.

Two examples of physiological rhythm regressors. Each graph represents the time course of the power of a specific frequency band convolved with the HRF. (a) For patient 8, fluctuation of the alpha, beta, theta and delta power. Note the high delta and theta power when the alpha power is low, suggesting that the patient was drowsy or sleepy. (b) For patient 6, fluctuation of the alpha, beta, theta and delta power and time course of spindles. The patient slept: there is a large number of spindles, large amplitude and variability of the theta and delta bands. The power of the alpha band remains low.

Fig. 4.

Correlation between BOLD and alpha power. (a) Individual results (patient 7). A positive correlation was seen mainly over the thalami, right caudate nucleus, anterior and posterior cingulate gyri and small bifrontal areas. A negative correlation was mostly observed in the occipital lobes. (b) Group analysis. A significant positive correlation was obtained in the thalami and putamen. A negative correlation was obtained in the occipital lobe, inferior parietal lobule, precentral gyrus, inferior frontal gyrus and middle frontal gyrus, bilaterally.

Fig. 5.

Correlation between BOLD and theta power. (a) Individual results (patient 1). A positive correlation was observed bilaterally over the putamen, insula and parasagittal area. The negative correlation was more predominant and bilateral over the cuneus, anterior and posterior cingulate gyrus, inferior parietal areas and superior temporal gyrus. (b) Individual results (patient 3). The negative correlation was predominant and bilateral over the cuneus, anterior cingulate gyrus, inferior parietal areas, superior temporal and inferior frontal gyrus. A periventricular and parasagittal activation was observed.

Fig. 6. Correlation between BOLD and sleep spindles. (a) Individual results (patient 12). Positive correlation was observed over both putamen and lateral part of the right thalamus. No negative correlation was seen. (b) Group analysis. A significant positive correlation was obtained in the thalami and in both putamen. No negative correlation was observed.

Fig. 7.

Comparison of alpha (A) and theta (B) t -maps obtained with a separate GLM analysis (top) and with a common GLM analysis (bottom) in subject 3. (A) Alpha t -map. The typical positive correlation in the thalami and negative correlation in the occipital lobes is common to both methods. A decrease of significant BOLD correlation is obtained in bilateral frontal and parietal areas when comparing separate with common analyses (top to bottom). (B) Theta t -map. The negative correlation in bilateral parietal, temporal lobes and in left frontal lobe is common. Clear decrease of the positive correlation obtained in bilateral insula, thalami and putamen. In (A) and (B), in the top, results for one rhythm mixed BOLD effects of the other rhythms having a time course correlated to their own. At the bottom, when the fluctuations of the other rhythms are used as confounds, results reflect specific BOLD changes related to the rhythm studied. For example the parietal negative correlation is present in both alpha and theta in the top maps, whereas the analysis with a common GLM finds that it is best attributed to theta alone.

Table 1

Group characteristics of subjects

Subjects	Gender	Age (years)	Interictal events		Number of runs	Alpha band (Hz)	Antiepileptic drugs
			Number	Localization			
(A) Subjects studied for alpha, beta, theta and delta rhythms							
1	Male	47	3	Bi temporal	9.3–11.7	10	Valproic acid 1500 mg, clobazam 20 mg
2	Male	52	1	L temporal	8.8–9	12	Carbamazepine 1300 mg, clobazam 10 mg, phenytoin 200 mg
3	Male	32	1	R temporal	9.3–9.8	12	Gabapentin 2400 mg, carbamazepine 1000 mg
4	Male	22	4	R temporoparietal	8.8–9.8	9	Carbamazepine 400 mg, clobazam 10 mg
5	Male	22	3	Bi frontal	11.2–11.7	9	Topiramax 100 mg, lamotrigine 600 mg, levetiracetam 3000 mg
6	Female	12	0	R centroparietal	11–11.2	6	Clobazam 10 mg, carbamazepine 800 mg
7	Male	29	4	Bi temporal	9.3–9.8	12	Carbamazepine 1000 mg, lamotrigine 450 mg
8	Male	40	6	R temporal	9.6–9.8	13	Carbamazepine 1000 mg, clobazam 10 mg
9	Male	41	6	L temporal	8.8–9.8	10	Oxcarbazepine 1200 mg
10	Male	17	0	L temporal	9.8–10.3	8	Valproic acid 875 mg
11	Male	46	5	L temporal	8.8–12	12	Topiramate 50 mg
Mean	10M/1F	32.7 ± 13					
Subjects	Gender	Age (years)	Interictal events		Number of spindles	Number of runs with spindles	Antiepileptic drugs
(B) Subjects studied for sleep spindles							
6	Female	12	0	R centroparietal	145	6	Clobazam 10 mg, carbamazepine 800 mg
9	Male	41	2	L temporal	18	4	Oxcarbazepine 1200 mg
12	Male	46	3	R frontotemporal	123	10	Carbamazepine 1200 mg, clobazam 10 mg
13	Male	30	5	R temporal	15	3	None
14	Female	30	5	L frontotemporal	11	5	Lamotrigine 300 mg
15	Male	19	77	R frontal	146	12	Clobazam 10 mg
Mean	4M/2F	29.7 ± 13					

Table 2

Brain areas involved by positive and negative correlation between BOLD and physiological rhythms

Subjects	Band power $\mu\text{V}^2/\text{Hz}$ (mean $\pm$ SD)	Occi	Thal	Lpar	Rpar	Ant cing	Post cing	L Inf frontal	R Inf frontal	Ltemp	Rtemp
<i>(A) Alpha, beta, theta and delta</i>											
Alpha											
1	1.72 $\pm$ 0.98	-7.2	-	-11.2	-7.8	5.5	8.3	6.6/-7.2	6.5/-8.7	-	-
2	12.92 $\pm$ 8.21	-5.2	-	3.6/-5.6	-6	-	5.2	-4.8	-4.9	-	-
3	7.68 $\pm$ 6.4	-6.6	6.3	-4.3	-4.4	-	-	4.7/-4.3	-	-	-
4	3.0 $\pm$ 1.84	-7.2	4.1	-4.5	-3.8	-	-	-4.6	-4.3	-3.7	-4
5	0.32 $\pm$ 0.27	-	3.6	-	-	-	-	-	-	-	-
6	3.64 $\pm$ 1.95	-	-	-4.7	-4.2	-	-	-	-	-	-
7	1.55 $\pm$ 2.79	-12.9	8.9	-5.6	-6.7	-	-5.6	-8.6	-8	-5.8	-6
8	5.91 $\pm$ 11.67	-16.8	11.9	-	-	-6.1	-	-15.8	-12.3	-8.1	-9.6
9	2.34 $\pm$ 4.59	-7.3	3.3	-	-	-	-	-	-	-3.9	-
10	1.65 $\pm$ 1.87	-	-	-	-	-	-	-5.8	-6.9	-	-
11	4.23 $\pm$ 5.34	-16.5	15.1	-16	-14.3	-	-	-14.5	-12	11.7/-9.1	11.4/-8.5
Beta											
1	0.33 $\pm$ 0.15	-	-	-	-	-	-	-	-	-	-
2	0.18 $\pm$ 0.09	-	-	-	-	-	-	-	-	-	-
3	0.19 $\pm$ 0.09	-	-	-	-	-	-	-	-	-	-
4	0.11 $\pm$ 0.06	-	-	-	-	-	-	-	-	-	-
5	0.08 $\pm$ 0.07	-	-	-	-	-	-	-	-	-	-
6	0.22 $\pm$ 0.09	-4.6	-	4.8	-	-	-	4.6	-	5.2	-
7	0.25 $\pm$ 0.12	-	-	-	-	-	-	-	-	-	-
8	0.11 $\pm$ 0.08	-	-	-	-	-	-	-	-	-	-
9	0.14 $\pm$ 0.11	-	-	-	-	-	-	-	-	-	-
10	0.4 $\pm$ 0.23	-	-	-	-	-	-	-	-	-	-
11	0.74 $\pm$ 0.6	-	-	-	-	-	-	-	-	-	-
Theta											
1	3.76 $\pm$ 2	-5.3	4.5	-6.3	-6	5.2/-3.9	-	5/-4.4	-	-3.9	-4.3
2	4.05 $\pm$ 2.2	4.5	-	-4.2	-3.8	-3.9	-	-4	-3.6	-	-
3	2.7 $\pm$ 1.7	-6.5	-	-5.5	-5.8	-4.3	-	-5.5	-4	-4.6	-5.5
4	2.21 $\pm$ 1.4	-6	6.5	6.1/-7.6	6.6/-7.6	5.9	5.6	-6.6	4.7/-5.5	5.5/-6.3	-4.9
5	1.96 $\pm$ 1.45	3.8	4.7	-	-	-	-	-	-4	-	-
6	25.57 $\pm$ 17.2	-	-	-5.2	-4.5	-	-	-4.6	-	-	-
7	1.9 $\pm$ 1.33	-12	-	-6.5	-6.5	-8.3	-	-8.8	8.7/-6.8	-4.6	-4.8
8	2.03 $\pm$ 1.87	-6.2	5	-6.7	-3.9	-	-	-6.1	-5.3	-	-
9	3.24 $\pm$ 2.39	-3.8	-	-	-	-	-	-3.8	-3.4	-	-
10	2.66 $\pm$ 1.78	-	-	-4.2	-5.2	-4.1	-4.6	-	-3.6	-	-
11	9.14 $\pm$ 7.83	-	-	5.5	5	-	-	-	-	-4.4	-4.3
Delta											

Subjects	Band power $\mu\text{V}^2/\text{Hz}$ (mean $\pm$ SD)	Occi	Thal	Lpar	Rpar	Ant cing	Post cing	L Inf frontal	R Inf frontal	Ltemp	Rtemp
1	3.76 ± 2	-4.6	-	-	-	-	-	-	-	-	-
2	6.79 ± 3.72	-	-	-	-	-	-	-	-	-	-
3	3.65 ± 2.4	-	-	4.4	5.2	5.3	-	-3.8	-4.1	-	-3.8
4	2.23 ± 1.23	-	-	-	-	-	-	-	-	-	-
5	8.17 ± 8.86	-	-	-	-	-	-	3.5	3.9	-	-
6	191.26 ± 193.24	-	-	-	-	-	-	-	-	-	-
7	2.87 ± 1.72	7.5	5.5	-	-	6.5	-	7.2	7.7	5.7	5.4
8	5.6 ± 6.5	-	-	-	-	-	-	5.8	5.5	-	6.2
9	7.3 ± 6.07	6.8	-	6.5	-	6.6	-	-	6.8	-	-
10	15.93 ± 18.54	-4	-	-	-	-	-	3.8	4.8	-	-
11	23.18 ± 22.05	-	4.2	4	5	-	-	-	-	-	4.8

Subjects	Occi	Thal	Put	Caud	Lpar	Rpar	Lfront	Rfront	Ltemp	Rtemp
<i>(B) Sleep spindles</i>										
Spindles										
1	-7.2	3.2	-	3.6	-	-	-3.5	-	-	4.1
2	-	-	-	-	-	-	-	-	-	-
3	-	3.6	4.4	-	-	-	-	-	-	4.8
4	-	-	4	-	-3.4	-	-	5.1	3.4	4.7
5	-	-	-	-	-	-	-	-	-	-
6	-	10.8	8.02	3.6	-7.6	-	-8	-10.6	7.2/-7.1	5

Positive and negative (italic bold font) *t*-value obtained for each patient over the different specific brain areas were reported in the table.

Table 3

Group analysis of the effect of alpha power variation and spindles on BOLD

	Correlation	Anatomical region	Hemisphere	Peak	X	Y	Z	Volume (cm ³)	p-value
Alpha	Positive	Thalamus, putamen	Bilateral	6.4	4	-22	9	53	0.0001
	Negative	Cuneus, precuneus, inferior temporal gyrus, middle occipital gyrus	Bilateral	-6.2	-57	-22	43	100	0.0001
Spindles	Positive	Inferior Parietal Lobule, precentral gyrus, inferior frontal gyrus, middle frontal gyrus	Left						
		Inferior parietal lobule, paracentral parietal lobule, precentral gyrus, inferior frontal gyrus, middle frontal gyrus	Right	-5	53	2	30	18	0.001
		Thalamus	Left	4.5	-14	-10	6	0.7	0.007
		Putamen	Right	3.7	19	-10	5	0.1	0.011
Negative	Negative		Left	3.4	-29	-3	7	0.1	0.012
			Right	3.6	28	-7	13	0.05	0.012
			-	-	-	-	-	-	-

Location of activated clusters in stereotactic space (MNI: X, Y, Z).